WHOLE BRAIN GROUP NETWORK ANALYSIS USING NETWORK BIAS AND VARIANCE PARAMETERS

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ABSTRACT

Effect of different diseases on the brain can be studied and analyzed using brain's complex functional and structural connectivity network. Many complex network measures have been used for this purpose in the literature. In this paper, we have introduced a new mechanism for the analysis of the brain connectivity network. In our framework, using a population of healthy subjects and patients, the true connectivity network, and each subject's bias and variance are estimated. These parameters have been used to design a procedure for the comparison of two groups of brain networks. We have used our introduced measures for the comparison of the resting state functional MRI network of pediatric Tuberous Sclerosis Complex (TSC) patients and healthy subjects. We have shown that using our introduced measure, a significant difference between the two groups can be found. In addition, we have compared our findings with a three well known complex network measures.

Index Terms— Functional connectivity, resting state fMRI, Connectivity graph, Parcellation, Tuberous Sclerosis Complex

1. INTRODUCTION

Human brain can be considered as a complex functional and structural network [1]. Graph theory has been widely utilized for the analysis and characterization of the brain connectivity network. To this end, using a measure, connectivity of different parts of the brain are calculated and used to create a functional or structural connectivity matrix of the brain [2]. Recently and in different studies, group analysis have been utilized to analyze effect of diseases on the brain network [3]. For this purpose, a series of complex network measures have been used to analyze the functional or structural connectivity networks of the brain. Using these measures, the effect of different diseases on integration, segregation, centrality, and resilience of each node and also the whole brain network has been studied [4]. In this paper, we introduce a new measure which can be used to analyze brain networks. In the new framework, first, by using the population of the networks, the true network, bias and variance of each one of the networks are estimated based on the Expectation-Maximization (EM) algorithm. Then, the estimated bias and variance parameters are used for the group analysis to compare the group of controls and patients. We have used our new measure to compare the functional network of a group of pediatric Tuberous Sclerosis Complex (TSC) patients with age matched healthy subjects. TSC is a neurologic disorder and patients present with severe epilepsy, cognitive impairment and neurobehavioral abnormalties, particularly autism [5]. In several studies, abnormalities in the white matter of TSC patients including dys-myelination in the white matter tracts have been reported [6]. However, there is a limited knowledge on functional and structural connectivity in pediatric TSC patients.

2. METHODS

Assume that the connectivity matrix W_j is generated for each one of the patients and healthy subjects in a population with J members. For each network j, w_{mnj} indicates the weight of the link that connects the regions m and n. We assume that there are L nodes (regions) in each one of the networks. In the literature, complex networks measures have been used to analyze the differences of the networks between the patients and controls. For this purpose, using each one of the measures, global or local organization of the networks are characterized and then population of patients and healthy subjects are compared.

2.1. True Brain Network

All of the above mentioned measures use graph features to compare different networks. However, in our approach, we consider each one of the connectivity matrices as a variation of the true brain network. Following the approach in [7, 8], we model the variation in the following form:

$$w_{mnj} = \tau_{mn} + \beta_j + \epsilon_{mnj} \quad (1)$$

In this formulation τ is the true brain network and τ_{mn} is the weight of the link between the nodes m and n in the true brain network. Also, β is the vector of bias of different networks in the population where β_j shows the bias of j-th network and

ϵ is the error where ϵ_{mnj} denotes the error in the weight of the link between nodes m and n. It is assumed that the error has an uncorrelated normal distribution $\epsilon_{mnj} \sim N(0, \sigma_j^2)$. Thus, we characterize j-th brain network in our population with a bias β_j from the true brain network and a variance σ_j^2 which models the errors. We assume that the joint distribution of the weights given the default network and each network's parameters have the following form:

$$Pr(w|\tau, \sigma, \beta) = \prod_{j=1}^{J} \prod_{m=1}^{L} \prod_{n=1, n<m}^{L} \phi\left(\frac{w_{mnj} - (\tau_{mn} + \beta_j)}{\sigma_j}\right) \quad (2)$$

where $\phi\{.\}$ is the pdf with normal distribution $N(0, 1)$. We assume that brain networks of different subjects in the population are independent. In addition, we also assume that the link weights in the network are independent. Because of the symmetrical form of the network, the elements of the matrix are not independent and therefore, we need to use lower triangular part or upper triangular part of the network matrices. The true network is not known and maximization of complete data likelihood can not be used to estimate the bias and variance of each one of the networks in the population. Thus, the EM algorithm is used to estimate the true brain network, bias, and variance of each one of the networks. It should be mentioned that there is no assumption about the weight values. For example, one of the problems of resting state fMRI (rsfMRI) analysis is the negative correlations and many complex network measures work on positive or negative weights. Thus, in many methods, either the negative values are eliminated or two different networks are considered for negative and positive connections [9]. Our aim is to find the bias and variance of each one of the networks. Using the EM algorithm at each iteration t, the expectation steps σ and τ are computed using the following two equations:

$$\frac{1}{(\sigma^2)^{(t)}} = \sum_{j=1}^{J} \frac{1}{(\sigma_j^2)^{(t)}}$$
$$\tau_{mn}^{(t)} = \frac{\sum_{j=1}^{J} (w_{mnj} - \beta_j^{(t)})/(\sigma_j^2)^{(t)}}{1/(\sigma^2)^{(t)}} \quad (3)$$

Then, in the maximization step using the results given in Eq. 3, estimation of β_j for each one the networks is updated using the following equation:

$$\beta_j^{(t+1)} = \frac{1}{L(L-1)/2} \sum_{n=1, n<m}^{n=L, m=L} (w_{mnj} - \tau_{mn}^{(t)}) \quad (4)$$

Moreover, estimation of σ_j for each one the networks is updated using the following equation:

$$(\sigma_j^2)^{(t+1)} = (\sigma^2)^{(t)} + \frac{1}{L(L-1)/2} \sum_{n=1, n<m}^{n=L, m=L} \left(w_{mnj} - \beta_j^{(t+1)} - \tau_{mn}^{(t)}\right)^2 \quad (5)$$

Using this framework, the parameters are updated iteratively until convergence is obtained which is guaranteed by using EM algorithm. Last but not least, we initialize the bias and variance parameters to zero and one, respectively.

2.2. Distance Calculation

After the calculation of the bias and variance of each network, these parameters will be used for the analysis of the networks. In this work, we focus on the application of the framework for the group analysis. Without loss of generality, it can be assumed that the networks of subjects $j \in \{1, ..., J_1\}$ and $j \in \{J_1 + 1, ..., J\}$, indicate healthy subjects and patient, respectively. It is possible to compare bias and variance of two groups independently, however, we are more interested to use both bias and variance parameters in the comparison of the groups. To this end, for the controls (C) and patients (P), the average bias are computed using the following equations:

$$\bar{\beta}_P = \frac{1}{J_1} \sum_{j=1}^{J_1} \beta_j$$
$$\bar{\beta}_C = \frac{1}{J_2 - J_1} \sum_{j=J_1+1}^{J} \beta_j \quad (6)$$

where $\bar{\beta}_C$ and $\bar{\beta}_P$ denote average bias of controls and patients, respectively. Moreover, using the following equations, the average variance of controls $\bar{\sigma}_C^2$, and the average variance of patients $\bar{\sigma}_P^2$, can be computed:

$$\bar{\sigma}_C^2 = \frac{1}{J_1} \sum_{1}^{J_1} \left(\sigma_j^2 + \left(\bar{\beta}_C - \beta_j\right)^2\right)$$
$$\bar{\sigma}_P^2 = \frac{1}{J_2 - J_1} \sum_{j=J_1+1}^{J} \left(\sigma_j^2 + \left(\bar{\beta}_P - \beta_j\right)^2\right) \quad (7)$$

Now, it is possible to directly compare the Gaussian probability distribution of the controls and patients using any probability distance measure. In this paper, we use symmetrized Kullback-Leibler divergence (SKLD) for the comparison of the two groups which can be defined as [10]:

$$S_D = KLD(N_P||N_C) + KLD(N_C||N_P) \quad (8)$$

where $KLD(N_1||N_2)$, the Kullback-Leibler divergence (KLD) of Gaussian probability distribution of group one and two is:

$$KLD(N_1||N_2) = \frac{1}{2}\left(\log\frac{(\bar{\sigma}_2^2)}{(\bar{\sigma}_1^2)} + \frac{(\bar{\sigma}_1^2)}{(\bar{\sigma}_2^2)} + \frac{(\bar{\beta}_2 - \bar{\beta}_1)^2}{\bar{\sigma}_2^2} - 1\right) \quad (9)$$

2.3. Complex Network Measures

There are different types of complex network measures that can be used for the analysis of the brain network. In this

paper, we compared our findings with 3 well known measures that are usually considered for this purpose. The considered measures are: Total connection strength (K), Overall weighted clustering coefficient (C), and Overall weighted transitivity (T) [4]. For each subject, K_j, C_j, and T_j can be computed using the following set of equations:

$$K_j = \frac{1}{L}\sum_{m,n} w_{mnj}$$
$$C_j = \frac{1}{L}\sum_{m} \frac{\sum_{n,k}(w_{mnj}w_{mkj}w_{nkj})^{(\frac{1}{3})}}{(\sum_n w_{mnj})(\sum_n w_{mnj}-1)}$$
$$T_j = \frac{\sum_{m,n,k}(w_{mnj}w_{mkj}w_{nkj})^{(\frac{1}{3})}}{\sum_m(\sum_n w_{mnj})(\sum_n w_{mnj}-1)} \quad (10)$$

Similar to our approach, for each one of these complex network measures, and also for the group of patients and controls, the average can be computed and their difference can be used for the analysis of the group differences. We define these differences as K_D, C_D and T_D.

2.4. Statistics

After finding the differences between the two groups using any measure, the differences should be examined using a statistical test. In this paper, we have used the permutation test for the analysis of the group differences. To this end, first, the distance between the two groups are computed using each one of the measures. Then, subjects are randomly divided to two groups with J_1 and $J - J_1$ subjects and the difference between the two groups are computed for each one of the measures. The procedure is repeated R times to find S_D^r, K_D^r,C_D^r and T_D^r for each $r \in \{1, \ldots, R\}$. Finally, we calculate p-value of measure X using $p_X = \frac{R-\sum_r H(X_D - X_D^r)}{R}$ where H is the step function. In this formulation, the number of times that the difference of the measures, between two randomly generated groups, is larger than the difference between the controls and the TSC patients, is used to estimate the p-value. In the next section, we use this strategy for the evaluation of different measures.

3. RESULTS

Structural MRI and rsfMRI were carried out in 22 subjects with TSC (age range 3-24 years, mean age 11.4), and in 18 age-matched controls on a 3T Siemens scanner. For rsfMRI, sequences with TR ranging from 2400ms to 3000ms were used. T1-weighted MPRAGE images of each subject were automatically segmented by label fusion into 128 cortical/sub-cortical structures using the IBSR datasets [11]. The fusion algorithm is an extension of STAPLE algorithm [12]. Figure 1(a) shows parcellation and segmentation of an axial slice through the brain based on 114 cortical and subcortical grey matter structures. A series of pre-processing steps were applied to the rsfMRI data of each subject. Head motion was corrected by rigid registration of each volume to the average of all volumes, and each motion corrected volume was spatially smoothed using a 8-mm full-width half-maximum (FWHM) Gaussian kernel. T1- weighted images and their segmentation were registered to the average of the head motion corrected rsfMRI images. Using a regression model, linear and quadratic trends, the averaged signal over the whole brain, the averaged signal over the ventricles, and the averaged signal over the deep white matter were removed [3]. Finally, the time series were band pass filtered by retaining frequencies between 0.01-0.08Hz.

For each one of cortical/sub-cortical grey matter structures, the average pre-processed time signal was utilized to construct a weighted connectivity graph for each subject, based on Pearson's correlation. In this paper, we focus on positive connectivity to be able to compare our findings with the results of other complex network measures. We have used our approach to estimate the true connectivity matrix of brain network which is shown in Figure 1(b). In addition, Figures 1(c) and 1(d) show a sample connectivity matrix of TSC patient and healthy subject. It can be seen in the figure that the connectivity matrix of healthy subjects and the estimated true connectivity matrix are similar. We applied a group difference analysis using the permutation test for our introduced method and also for each one of the complex network measures. For the permutation test and for each one of the measures, we have used 10,000 random permutations and a significance threshold of 0.05 for the tests. Statistical analysis using the permutation test shows a significant difference between patients and healthy subject using our approach ($p_S < 0.05$). In addition, the permutation test shows a significant difference between TSC patients and controls for the total connection strength and overall weighted clustering coefficients, ($p_C, p_K < 0.05$). However, the difference between the two groups is not significant based on an overall weighted transitivity ($p_T > 0.08$). These finding shows that the introduced measure can be used for the connectivity network analysis.

4. CONCLUSIONS

We have introduced a measure for the comparison of the connectivity matrix of a group of patients and healthy subjects. In our framework, based on the population of subjects, the true brain network, bias, and variance of each one of the subjects are estimated where these parameters can be used for the group analysis. We performed resting state functional connectivity group analysis of pediatric TSC patients and controls. Differences in connectivity could help explain the neurological phenotype in patients with TSC, as decreased long-range connectivity is thought to be associated with autism spectrum disorders. The statistical analysis using permutation test on our introduced measure shows a significant difference

between the networks ($p < 0.05$). In addition, we have used three well known complex network measures for the analysis of the same subjects. Two of the complex network measures show a significant difference between functional connectivity in TSC patients compared to controls ($p < 0.05$). It should be pointed out that we have used our method for the global network analysis, however, it is also possible to use our method to find the local differences between patient population and healthy subjects, given that there is no global difference between the two groups.

5. ACKNOWLEDGMENTS

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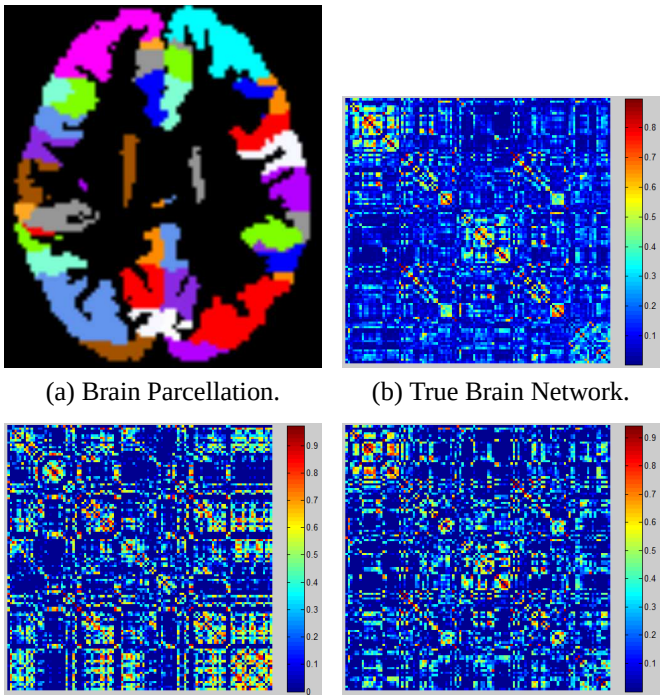

(a) Brain Parcellation. (b) True Brain Network.

(c) Sample TSC Network. (d) Sample Healthy Network.

Fig. 1. Brain parcellation and connectivity matrices. (a). Parcellation and segmentation of an axial slice based on 114 cortical and sub-cortical grey matter structures. (b). Estimated true brain network. (c). Network of a patient with TSC. (d). Network of a healthy subject.

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